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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,417	11/29/2000	Tony Kouzarides	620-118	3566

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/13/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/700,417	Kouzarides
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____ .

2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-13 and 24-26* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *1-10* is/are allowed.

6) ☒ Claim(s) *11-13 and 24-26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. Claims 1, 3, 4, 8, 9, and 12 have been amended. Claims 14-18 have been canceled. Claims 24-26 have been amended. Claims 1-13 and 24-26 are pending and under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections Maintained

3. The rejection of claim 12 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record. Namely, in the case of the agent which is not peptidyl, there is no link to the active method steps.

The rejection of claims 11 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons of record. The rejection of newly added claims 24-26 is made for the same reasons of record.

(A)As drawn to pharmaceutical compositions

Claim 11 is drawn to an agent which affects E2F acetylation formulated into a composition including a pharmaceutically acceptable excipient. The specification does not provide an objective evidence that an agent which interferes with the acetylation of E2F could be used in a method of treating a disorder of cell growth. Although it is known in the art that deregulated expression and altered function of genes involved in cell cycle regulation contribute to the pathogenesis of cancer (Hartwell et al, Science, 1994, Vol. 266, pp. 1821-1828), it cannot be anticipated that agents which interfere with the acetylation of E2F could be used in a

pharmaceutical composition for the treatment of cell growth disorders. The art teaches that E2F is regulated by binding with "pocket proteins" such as the retinoblastoma tumor suppressor protein (Ferreira et al, PNAS, 1998, Vol. 95, pp. 10493-10498) and is responsible for the transcription of genes needed for entry into S phase (Nevins et al, Science, 1992, vol. 258, pp. 424-429). It has been reported that overexpression of E2F in fibroblasts induced premature S-phase entry resulting in apoptosis, and that downregulation of E2F activity leads to resistance to apoptosis (Bargou et al, Journal of Experimental Medicine, 1996, Vol. 183, pp. 1205-1213). Thus, agents, such as peptides which compete with E2F for binding to P/CAF will decrease the acetylation and transcriptional activity of E2F, and increase resistance to apoptosis. The specification has not identified a disease associated with enhanced apoptosis which could benefit by administration of an agent which decreases apoptosis. Further, it appears that the agents are not selective for diseased cells nor would it be expected that the pharmaceutical composition or medicament would act only on diseased cells since E2F occurs ubiquitously. In addition, pharmaceutical compositions must be delivered into the circulation that supplies the diseased tissue or organ and be taken up by the diseased cells at a sufficient concentration and for a sufficient period of time to induce a therapeutic effect. The specification does not teach how to make/use a pharmaceutical composition targeted to tissues or organs undergoing enhanced apoptosis. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful treatment. The pharmaceutical composition may be inactivated in vivo before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the composition. In addition, the composition may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, or it may be absorbed by fluids, cells and tissues where the composition has no effect, and circulation into the target area may be insufficient to carry the composition and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples

which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of using the claimed agents in pharmaceutical compositions or medicaments for the treatment of disease with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation in order to practice the claimed invention.

Applicant argues that the composition comprising a pharmaceutically acceptable excipient does not imply any necessity for the composition to be used in a method of treatment. This has been considered but not found persuasive, as the specification does not teach any alternative use that is specific for the composition of any of claims 1, 2, 3, 4, 5 and 9 formulated with a pharmaceutically acceptable excipient.

(B)As drawn to peptide fragments

Claims 24 is drawn to a peptide fragment of E2F or P/CAF of about 40 amino acids or less and comprises the lysine residues found at positions 117, 120, and 125 of wild-type E2F, said fragment modulating the interaction between E2F and P/CAF. Claim 25 specifically embodies the peptide of claim 24 wherein said peptide is 20 amino acids in length. Claims 26 is drawn to the isolated nucleic acid encoding the peptide of claim 24. The specification teaches that a fragment of E2F1 corresponding to amino acids 89-432 was acetylated by interaction with P/CAF. The specification further teaches that the E2F1 lysine residues of 117, 120 and 125 were acetylated by P/CAF. The specification does not teach any peptide fragment which interferers with or modulates this acetylation. It is known in the art that physical interaction between E2F1 and a histone acetylase transcriptional coactivator is complex. For example, Trouche et al (Nucleic Acids Research, 1996, Vol. 24, pp. 4139-4145) teach that three modules of E2F1 interact with the transcriptional coactivator CBP, and that module 3, although required for CBP binding, is not sufficient for CBP interaction (Trouche et al, page 4143, column 2, lines 24-27). Trouche et al further suggest that additional undisclosed residues within modules 1 and 2, which are not co-linear within E2F1, are required for CBP contact. Thus it can be concluded

that a peptide fragment consisting of module 3 would not be able to bind to CBP or to interfere with the binding of E2F with CBP. The specification does not demonstrate that a smaller fragment of 40 amino acids comprising lysine residues 117, 120 and 125 would be sufficient to bind P/CAF and would bind P/CAF in preference to E2F1 thus interfering with the acetylation of wild-type E2F. Although it can be assumed that residues 117 through 125 contact P/CAF, it cannot be assumed that peptides comprising residues 117 through 125 of E2F1 within a fragment smaller than residues 89-432 of E2F1 will be sufficient to interact with P/CAF and compete with wild-type E2F1 for binding to P/CAF. Given the lack of guidance in the specification and the teachings of Trouche et al regarding the complexity of binding of E2F and P/CAF, one of skill in the art would be subjected to undue experimentation in order to practice the invention to the full scope of the claims.

Applicant has canceled claim 15-18 and substituted claims 24-26 which are drawn solely to fragments of E2F versus P/CAF. However, given the teachings of /Trouche et al on the complexity of the interaction between P/CAF and E2F, it cannot be anticipated that the fragment of claims 24 and 25 and the nucleic acid encoding the fragment of claim 24 will function to inhibit the acetylation of E2F for the reasons set forth above.

4. All other rejections and objections as set forth in Paper No. 12 are withdrawn.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
August 5, 2002

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